Synthesis and Biological Activity of a 3,5-Disubstituted-1,2,4-Oxadiazole Fungicide Containing 3-Pyrazole Group

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Abstract: In order to develop a new compound with novel structure and bactericidal activity. A series of 3,5-disubstituted-1,2,4-oxadiazole compounds containing pyrazole group were designed and synthesized. Their structures were confirmed by ^{1}H NMR and HRMS, their bactericidal activity were evaluated by against *rhizoctonia solani*, *gibberella zeae*, *botrytis cinerea* and *physalospora piricola.* Preliminary bioactivity test results indicated that compound $\mathbf{I_6}$ showed the highest bactericidal activity among them, the inhibition rates of compound $\mathbf{I_6}$ against the above four fungi were 87.56, 88.69, 86.38, 89.78, respectively.

1. Introduction

Effective use of pesticides is an important guarantee for grain production and increase[1]. However, due to unreasonable use of agricultural pesticides in the past, which not only lead to the resistance of pests, mites and fungi to pesticides, but also caused serious environmental pollution problems[2]. The development of pesticides with new chemical structures and mechanisms has become an important means to solve today's pest resistance problems.

Heterocyclic compounds containing oxygen and nitrogen atoms are particularly important in heterocyclic compounds[3], the 1,2,4-oxadiazole derivatives are five-membered heterocyclic compounds and have broad biological activities in medicines and pesticides[4-5]. Since 1,2,4-oxadiazole has various biological activities such as antibacterial, antihypertensive, insecticidal and herbicidal, it is often used as an effective active group in the design of medicines and pesticides[6-7]. The heterocyclic ring tends to have high biological activity, the oxadiazole ring in the 1,2,4-oxadiazole derivatives exhibits excellent insecticidal activity[8]. As a hotspot in the research and development of pesticides, new heterocyclic chemical pesticides are in the ascendant, new varieties are constantly coming out. Their structures are different, their mechanism of action and insecticidal effects are not the same, and more drug choices can be provided. In this paper we used tioxazafen as a lead compound, introduced pyridyl group to the 3 position, pyrazole and thiazole ring introduced to the 5 position of 1,2,4-oxadiazole, designed and synthesized a series of novel compounds having bactericidal activity.

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2. Design and Synthesis of the Target Compounds

2.1 Design of the Target Compound.

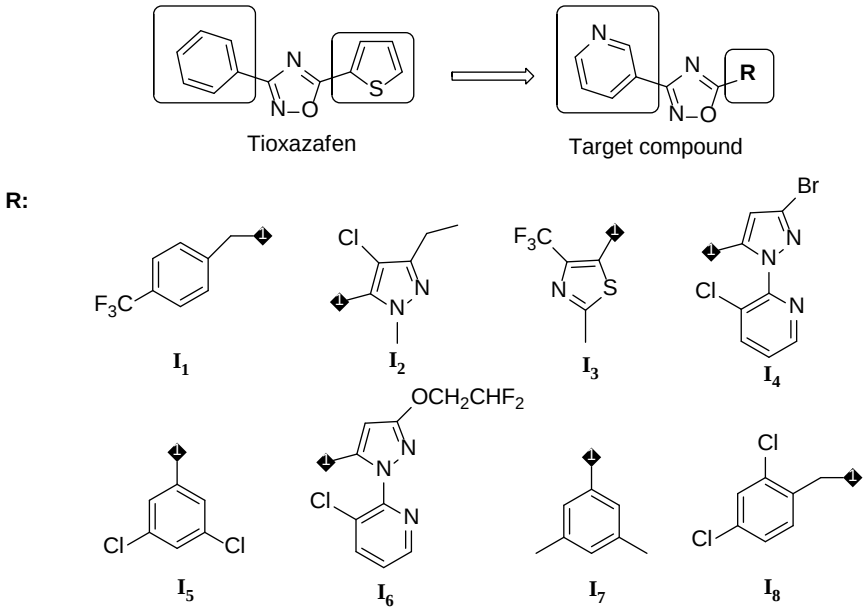

Figure. 1 Design strategy of target compounds

2.2 Synthesis of the Target Compounds.

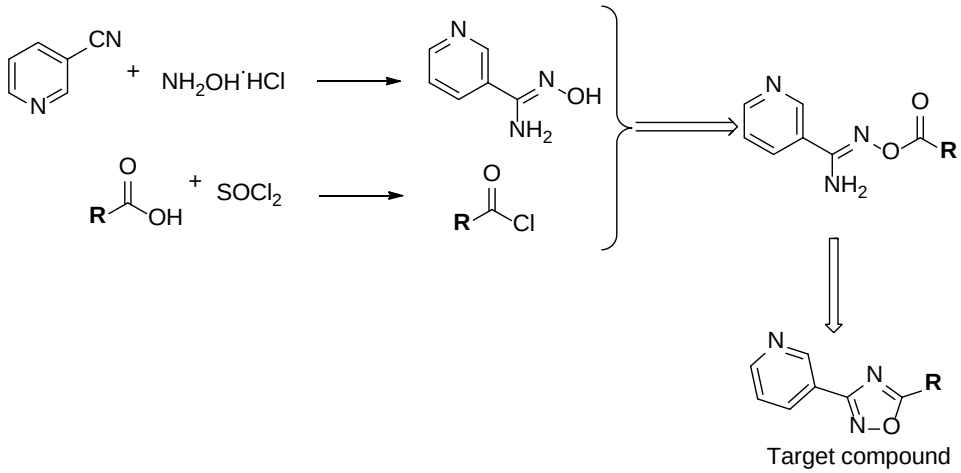

Figure. 2 Synthetic route of target compounds

2.2.1 Synthesis of compound I_1 as an example.

2.2.1.1 Synthesis of N'-hydroxynicotinimidamide.

To a solution of nicotinonitrile (10.4 g, 0.1 mol), triethylamine (12 g, 0.12 mol), hydroxylamine hydrochloride (14 g, 0.2 mol) in ethanol (150 mL), then the reaction mixture was stirred at 80℃ for 4 hrs, it was monitored by TLC until nicotinonitrile was consumed completely. Poured 200 mL of water into the reaction solution, after that the reaction mixture was filtered and the filter cake was dried to give N'-hydroxynicotinimidamide as a white powder(11.8g). Yield, 86%.

2.2.1.2 Synthesis of 2-(4-(trifluoromethyl)phenyl)acetyl chloride

Put 4-(trifluoromethyl)phenyl acetic acid(20.4 g, 0.1 mol), thionyl chloride(17.9 g, 0.15 mol) into toluene (150 ml) and stirred at 110℃ for 5 hrs, it was monitored by TLC until 4-(trifluoromethyl)phenyl acetic acid was consumed completely. The reaction mixture was

concentrated in vacuo to yield a light yellow oily liquid. Yield, 98.5%.

2.2.1.3 Synthesis of N'-(2-(4-(trifluoromethyl)phenyl)acetoxy)nicotinimidamide

Put N'-hydroxynicotinimidamide (6.9 g, 0.05 mol), triethylamine(10g, 0.1mol) into dichloromethane and stirred at room temperature, then 2-(4-(trifluoromethyl)phenyl)acetyl chloride(13.3 g, 0.06 mol) was added under water cooling. After that the mixture was stirred at room temperature for 3 hrs, it was monitored by TLC until N'-hydroxynicotinimidamide was consumed completely. Then 100ml of water was poured to the reaction system. The organic layer was washed with water, dried over by sodium sulfate, concentrated in vacuo. The residue was recrystallized from 150 ml methanol and dried to give a white solid (12 g). Yield, 75%.

2.2.1.4 Synthesis of 3-(pyridin-3-yl)-5-(4-(trifluoromethyl)benzyl)-1,2,4-oxadiazole

N'-(2-(4-(trifluoromethyl)phenyl)acetoxy)nicotinimidamide (16.2 g, 0.05 mol) was added in toluene(100 ml). Then the resulting mixture was heated at 110°C for 6 hrs, it was monitored by TLC until N'-(2-(4-(trifluoromethyl)phenyl)acetoxy)nicotinimidamide was consumed completely. Then the reaction mixture was concentrated in vacuo, After that, the residue was recrystallized from 80 ml methanol and dried to give 3-(pyridin-3-yl)-5-(4-(trifluoromethyl)benzyl)-1,2,4-oxadiazole a white powder(12 g). Yield, 76.3%.

2.3 Data for the Twenty Compounds

2.3.1 Data for the compound I_1

^{1}H NMR (500 MHz, DMSO-d6) δ (ppm) 9.24 (d, J = 2.2 Hz, 1H), 8.80 (dd, J = 4.9, 1.7 Hz, 1H), 8.42 (dd, J = 8.0, 2.1 Hz, 1H), 8.20 (d, J = 8.1 Hz, 2H), 7.72 (d, J = 8.2 Hz, 2H), 7.61 (d, J = 10.1 Hz, 1H), 4.89 (s, 2H). White powder; yield, 76.3%; mp, 136.3～138.2°C; HRMS: calculated for $C_{15}H_{10}F_3N_3NaO$ $[M+Na]^+$ 328.0674, found 328.0678

2.3.2 Data for the compound I_2

^{1}H NMR (500 MHz, DMSO-d6) δ (ppm) 9.23 (d, J = 2.2 Hz, 1H), 8.81 (dd, J = 4.8, 1.7 Hz, 1H), 8.42 (dt, J = 8.0, 2.0 Hz, 1H), 7.64 (dd, J = 8.0, 4.8 Hz, 1H), 4.22 (s, 3H), 2.62 (q, J = 7.5 Hz, 2H), 1.21 (t, J = 7.5 Hz, 3H). White powder; yield, 77.6%; mp, 91.5～93.4°C; HRMS: calculated for $C_{13}H_{12}ClN_5NaO$ $[M+Na]^+$ 312.0628, found 312.0631.

2.3.3 Data for the compound I_3

^{1}H NMR (500 MHz, DMSO-d6) δ (ppm) 9.18 (d, J = 2.2 Hz, 1H), 8.82 (dd, J = 4.9, 1.7 Hz, 1H), 8.38 (dt, J = 8.1, 2.0 Hz, 1H), 7.64 (dd, J = 8.0, 4.8 Hz, 1H), 2.84 (s, 3H). White powder; yield, 68.6%; mp, 142.2～143.5°C; HRMS: calculated for $C_{12}H_7F_3N_4NaOS$ $[M+Na]^+$ 335.0910, found 335.0907.

2.3.4 Data for the compound I_4

^{1}H NMR (500 MHz, DMSO-d6) δ (ppm) 8.88 (d, J = 2.1 Hz, 1H), 8.77 (dd, J = 4.8, 1.6 Hz, 1H), 8.65 (dd, J = 4.7, 1.5 Hz, 1H), 8.40 (dd, J = 8.1, 1.5 Hz, 1H), 8.14 (dt, J = 8.1, 2.0 Hz, 1H), 7.86 (s, 1H), 7.84 (dd, J = 8.1, 4.7 Hz, 1H), 7.58 (dd, J = 8.0, 4.8 Hz, 1H). White powder; yield, 76.8%; mp, 165.2～167.7°C; HRMS: calculated for $C_{15}H_8BrClN_6NaO$ $[M+Na]^+$ 424.9529, found 424.9533.

2.3.5 Data for the compound I_5

^{1}H NMR (500 MHz, DMSO-d6) δ(ppm) 9.27 (d, J = 2.1 Hz, 1H), 8.83 (dd, J = 4.9, 1.7 Hz, 1H), 8.47 (m, J = 8.0, 1.9 Hz, 1H), 8.21 (d, J = 1.9 Hz, 2H), 8.08 (t, J = 1.9 Hz, 1H), 7.67 (dd, J = 8.0, 4.8 Hz, 1H). White powder; yield, 75.4%; mp, 154.3 ～ 155.6°C; HRMS: calculated for $C_{13}H_7Cl_2N_3NaO$ $[M+Na]^+$ 313.9864, found 313.9869.

2.3.6 Data for the compound I_6

^{1}H NMR (500 MHz, DMSO-d6) δ (ppm) 8.92 (d, J = 2.1 Hz, 1H), 8.79 (dd, J = 4.8, 1.7 Hz, 1H), 8.63 (dd, J = 4.7, 1.6 Hz, 1H), 8.37 (dd, J = 8.2, 1.6 Hz, 1H), 8.17 (dt, J = 8.0, 2.0 Hz, 1H), 7.79 (dd, J = 8.1, 4.7 Hz, 1H), 7.60 (dd, J = 8.0, 4.8 Hz, 1H), 7.27 (s, 1H), 6.46 (t, J = 3.3 Hz, 1H), 4.60 (td, J = 14.9, 3.3 Hz, 2H). White powder; yield, 81.6%; mp, 106.8～109.2°C; HRMS: calculated for $C_{17}H_{11}ClF_2N_5NaO_2$ $[M+Na]^+$ 427.0948, found 427.0951.

2.3.7 Data for the compound I_7

^{1}H NMR (500 MHz, DMSO-d6) δ (ppm) 9.23 (d, J = 2.1 Hz, 1H), 8.81 (dd, J = 4.9, 1.6 Hz, 1H), 8.42 (dt, J = 8.0, 2.0 Hz, 1H), 7.80 (s, 2H), 7.64 (dd, J = 7.9, 4.8 Hz, 1H), 7.36 (s, 1H), 2.40 (s, 6H). White powder; yield, 75.7%; mp, 100.3～102.5°C; HRMS: calculated for $C_{15}H_{13}N_3NaO$ $[M+Na]^+$ 274.0956, found 274.0960.

2.3.8 Data for the compound I_8

^{1}H NMR (500 MHz, DMSO-d6) δ (ppm) 9.11 (d, J = 2.2 Hz, 1H), 8.76 (dd, J = 4.8, 1.8 Hz, 1H), 8.30 (dt, J = 7.9, 1.9 Hz, 1H), 7.70 (d, J = 2.1 Hz, 1H), 7.62 (dd, J = 8.4, 1.5 Hz, 1H), 7.58 (dd, J = 8.0, 4.7 Hz, 1H), 7.49 (dt, J = 8.3, 2.0 Hz, 1H), 4.59 (d, J = 1.6 Hz, 2H). White powder; yield, 70.6%; mp, 102.3～103.8°C; HRMS: calculated for $C_{14}H_9Cl_2N_3NaO$ $[M+Na]^+$ 328.0020, found 328.0023.

3.Bactericidal Activity

3.1 Bactericidal Activity of the Target Compounds Against *Rhizoctonia Solani, Gibberella Zeae, Botrytis Cinerea* And *Physalospora Piricola.*

According to ‘Pesticide indoor bioassay experimental guidelines, Fungicide’,
Using flat dish method to determinate the bactericidal activity of the eight target compounds.

4. Results and Discussion

Form the data in Table 1 we can see that the eight target compounds all have certain bactericidal activity against *rhizoctonia solani, gibberella zeae, botrytis cinerea* and *physalospora piricola.* Among them the Compound **I_1**, **I_2**, **I_3**, **I_4**, **I_6** exhibited excellent bactericidal activity, In particular, the inhibition rate of compound **I_6** at a concentration of 50ug/L against rhizoctonia s*olani, gibberella zeae, botrytis cinerea and physalospora piricola* were 87.56, 88.69, 86.38, 89.78 respectively, showed the highest bactericidal activity among them.

Table 1 Bactericidal activities of target compounds

Compound	Relative inhibition rate (%) 50ug/L			
	rhizoctonia solani	*gibberella zeae*	*botrytis cinerea*	*physalospora piricola*.
I_1	68.73	69.66	67.38	68.56
I_2	71.32	70.53	69.75	70.91
I_3	73.81	74.69	72.43	73.98
I_4	76.37	77.56	73.49	75.87
I_5	46.41	47.32	48.66	47.59
I_6	87.56	88.69	86.38	89.78
I_7	36.57	38.71	37.62	39.31
I_8	54.62	55.59	56.82	55.75

5. Conclusions

In summary, eight novel type oxadiazole compounds containing 3-pyridyl were designed and

synthesized and their structures were confirmed by ^{1}H NMR and HRMS. The preliminary bactericidal activity test revealed that the eight compounds showed certain activity against *rhizoctonia solani*, *gibberella zeae*, *botrytis cinerea* and *physalospora piricola*. Among them the Compound $\mathbf{I_1}$, $\mathbf{I_2}$, $\mathbf{I_3}$, $\mathbf{I_4}$, $\mathbf{I_6}$ exhibited excellent bactericidal activity, especially compound $\mathbf{I_6}$ showed the highest bactericidal activity against the above four fungi. These results indicated that when R was 1-ethyl-4-(trifluoromethyl)benzene, 4-chloro-3-ethyl-1,5-dimethyl-1H-pyrazole,2,5-dimethyl-4-(trifluoromethyl)thiazole, 2-(3-bromo-5-methyl-1H-pyrazol-1-yl)-3-chloropyridine,3-chloro-2-(3-(2,2-difluoroethoxy)-5-methyl-1H-pyrazol-1-yl)pyridine, these substituent groups contain a heterocyclic structure such as a pyrazole ring or a thiazole ring. This indicated that these heterocyclic structures might be a crucial factor to increase the bactericidal activity of the compounds. The present work revealed that the compound $\mathbf{I_6}$ could be used as novel lead compound for the development of new fungicide.

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